* * * * * * * * * * Welcome to STN International * * * * * * * * * *

| | | |
|---|---|---|
| NEWS 1 | | Web Page URLs for STN Seminar Schedule - N. America |
| NEWS 2 | | "Ask CAS" for self-help around the clock |
| NEWS 3 | May 12 | EXTEND option available in structure searching |
| NEWS 4 | May 12 | Polymer links for the POLYLINK command completed in REGISTRY |
| NEWS 5 | May 27 | New UPM (Update Code Maximum) field for more efficient patent SDIs in CAplus |
| NEWS 6 | May 27 | CAplus super roles and document types searchable in REGISTRY |
| NEWS 7 | Jun 28 | Additional enzyme-catalyzed reactions added to CASREACT |
| NEWS 8 | Jun 28 | ANTE, AQUALINE, BIOENG, CIVILENG, ENVIROENG, MECHENG, and WATER from CSA now available on STN(R) |
| NEWS 9 | Jul 12 | BEILSTEIN enhanced with new display and select options, resulting in a closer connection to BABS |
| NEWS 10 | Jul 30 | BEILSTEIN on STN workshop to be held August 24 in conjunction with the 228th ACS National Meeting |
| NEWS 11 | AUG 02 | IFIPAT/IFIUDB/IFICDB reloaded with new search and display fields |
| NEWS 12 | AUG 02 | CAplus and CA patent records enhanced with European and Japan Patent Office Classifications |
| NEWS 13 | AUG 02 | STN User Update to be held August 22 in conjunction with the 228th ACS National Meeting |
| NEWS 14 | AUG 02 | The Analysis Edition of STN Express with Discover! (Version 7.01 for Windows) now available |
| NEWS 15 | AUG 04 | Pricing for the Save Answers for SciFinder Wizard within STN Express with Discover! will change September 1, 2004 |
| NEWS 16 | AUG 27 | BIOCOMMERCE: Changes and enhancements to content coverage |
| NEWS 17 | AUG 27 | BIOTECHABS/BIOTECHDS: Two new display fields added for legal status data from INPADOC |
| NEWS 18 | SEP 01 | INPADOC: New family current-awareness alert (SDI) available |
| NEWS 19 | SEP 01 | New pricing for the Save Answers for SciFinder Wizard within STN Express with Discover! |
| NEWS 20 | SEP 01 | New display format, HITSTR, available in WPIDS/WPINDEX/WPIX |
| NEWS 21 | SEP 14 | STN Patent Forum to be held October 13, 2004, in Iselin, NJ |

| | |
|---|---|
| NEWS EXPRESS | JULY 30 CURRENT WINDOWS VERSION IS V7.01, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004 |
| NEWS HOURS | STN Operating Hours Plus Help Desk Availability |
| NEWS INTER | General Internet Information |
| NEWS LOGIN | Welcome Banner and News Items |
| NEWS PHONE | Direct Dial and Telecommunication Network Access to STN |
| NEWS WWW | CAS World Wide Web Site (general information) |

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* * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 20:49:15 ON 15 SEP 2004

=> file hcaplus
COST IN U.S. DOLLARS

| | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|

h eb c g cg b cg eb

FULL ESTIMATED COST 0.21 0.21

FILE 'HCAPLUS' ENTERED AT 20:49:22 ON 15 SEP 2004
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FILE COVERS 1907 - 15 Sep 2004 VOL 141 ISS 12
FILE LAST UPDATED: 14 Sep 2004 (20040914/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s antiarrhythmic? () atrial ) fibrillation
UNMATCHED RIGHT PARENTHESIS 'ATRIAL ) FIBRILLAT'
The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s antiarrhythmic? () atrial () fibrillation
         13326 ANTIARRHYTHMIC?
         22231 ATRIAL
             1 ATRIALS
         22231 ATRIAL
                 (ATRIAL OR ATRIALS)
          8211 FIBRILLATION
           173 FIBRILLATIONS
          8311 FIBRILLATION
                 (FIBRILLATION OR FIBRILLATIONS)
L1          62 ANTIARRHYTHMIC? (W) ATRIAL (W) FIBRILLATION

=> s l1 and potassium () block?
        542006 POTASSIUM
            15 POTASSIUMS
        542008 POTASSIUM
                 (POTASSIUM OR POTASSIUMS)
        527809 BLOCK?
           130 POTASSIUM (W) BLOCK?
L2            0 L1 AND POTASSIUM (W) BLOCK?

=> s l1 and potassium
        542006 POTASSIUM
            15 POTASSIUMS
        542008 POTASSIUM
                 (POTASSIUM OR POTASSIUMS)
L3            4 L1 AND POTASSIUM

=> s l3 and review/dt
       1757748 REVIEW/DT
```

h eb c g cg b cg eb

term sinus rhythm maintenance in flutter than AF. The relative specificity of class I and III AADs for flutter is explained by the newer concepts of arrhythmia mechanisms. Class III AADs would prolong refractory period without affecting conduction velocity, thus increasing wavelength.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> s antiarrhythmic? () supraventricular () arrhythmia?
         13326 ANTIARRHYTHMIC?
           658 SUPRAVENTRICULAR
         14787 ARRHYTHMIA?
L7           1 ANTIARRHYTHMIC? (W) SUPRAVENTRICULAR (W) ARRHYTHMIA?

=> s l7 and review/dt
       1757748 REVIEW/DT
L8           1 L7 AND REVIEW/DT

=> d l8, ibib abs, 1

L8   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
```

Full Text | Citing References

```
ACCESSION NUMBER:        1996:159635  HCAPLUS
DOCUMENT NUMBER:         124:277460
TITLE:                   Current topics on new class III antiarrhythmic drugs:
                         In special reference to clinical effects on
                         supraventricular arrhythmias
AUTHOR(S):               Iinuma, Hiroyuki; Kato, Kazuzo
CORPORATE SOURCE:        Cardiovascular Institute, Tokyo, Japan
SOURCE:                  Recent Progress in Electropharmacology of the Heart,
                         Proceedings of the International Satellite Symposium
                         of the 59th Annual Scientific Meeting of the Japanese
                         Circulation Society, Nagoya, Apr. 3-4, 1995 (1996),
                         Meeting Date 1995, 161-7.  Editor(s): Toyama, Junji;
                         Hiraoka, Masayasu; Kodama, Itsuo.  CRC: Boca Raton,
                         Fla.
                         CODEN: 62LYAD
DOCUMENT TYPE:           Conference; General Review
LANGUAGE:                English
AB   A review with 2 refs.


=> s antiarrhythmic? and cardiac () arrhymthia?
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        101846 CARDIAC
            48 CARDIACS
        101871 CARDIAC
                 (CARDIAC OR CARDIACS)
             1 ARRHYMTHIA?
             0 CARDIAC (W) ARRHYMTHIA?
L9           0 ANTIARRHYTHMIC? AND CARDIAC (W) ARRHYMTHIA?

=> s antiarrhythmic?  () cardiac? () arrhythmia?
         13326 ANTIARRHYTHMIC?
        103098 CARDIAC?
         14787 ARRHYTHMIA?
L10          8 ANTIARRHYTHMIC?  (W) CARDIAC? (W) ARRHYTHMIA?
```

h eb c g cg b cg eb

```
=> s l10 and review/dt
       1757748 REVIEW/DT
L11           2 L10 AND REVIEW/DT

=> d l11, ibib abs, 1-2

L11  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
```

Full Text | Citing References

```
ACCESSION NUMBER:         2000:896487  HCAPLUS
DOCUMENT NUMBER:          135:55245
TITLE:                    Clamikalant (Aventis)
AUTHOR(S):                O'Rourke, Stephen T.
CORPORATE SOURCE:         Department Pharmaceutical Sciences, North Dakota State
                          University, Fargo, ND, 58105-5055, USA
SOURCE:                   IDrugs (2000), 3(11), 1353-1357
                          CODEN: IDRUFN; ISSN: 1369-7056
PUBLISHER:                Current Drugs Ltd.
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 English
AB   A review with 57 refs.  Clamikalant is a cardioselective blocker of the
     ATP-dependent potassium channel (KATP) which is under development by
     Aventis Pharma (formerly Hoechst Marion Roussel) for the potential
     treatment of cardiac arrhythmia.  The sodium salt, HMR-1098, is in phase
     II trials.  Aventis plans for an i.v. prepn. of the drug to be launched in
     2004, and an oral prepn. to be available in 2005.  Clamikalant prevented
     ischemia-induced redns. in refractory period in dogs with ventricular
     fibrillation without significant hemodynamic effects or alteration in
     blood glucose levels.  HMR-1883 exerted an anti-arrhythmic effect in a
     model of isolated hearts from male White New Zealand rabbits, and
     indicated and did not interfere with post-ischemic hyperemia.
REFERENCE COUNT:          57    THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11  ANSWER 2 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
```

Full Text | Citing References

```
ACCESSION NUMBER:         2000:825976  HCAPLUS
DOCUMENT NUMBER:          134:320400
TITLE:                    Cardiac arrhythmias and drugs affecting intracellular
                          calcium ions
AUTHOR(S):                Honma, Nobuo; Hashimoto, Keitaro
CORPORATE SOURCE:         Department of Pharmacology, Yamanashi Medical
                          University, Japan
SOURCE:                   Clinical Calcium (2000), 10(11), 1413-1418
                          CODEN: CLCCEJ; ISSN: 0917-5857
PUBLISHER:                Iyaku Janarusha
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 Japanese
AB   A review with 2 refs. In the heart, Ca2+ concn. and transport are closely
     related to elec. conduction and impulse formation, as well as to
     myocardial contraction.  It is important to know how the an abnormality of
     intracellular Ca2+ concn. leads to cardiac arrhythmias.  This review
     focuses on cardiac arrhythmias and drugs which potentially affect
     intracellular Ca2+ and summarizes (1) the mechanisms of arrhythmias, (2)
     the target proteins of drug action, and (3) the introduction of new drugs.

=>
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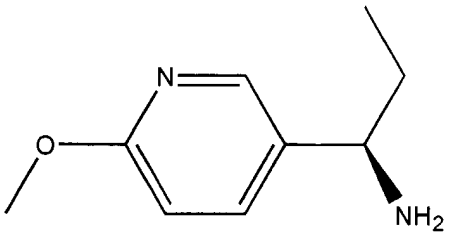
h eb c g cg b cg eb




1(R)-(6-Methoxypyridin-3-yl)propylamine

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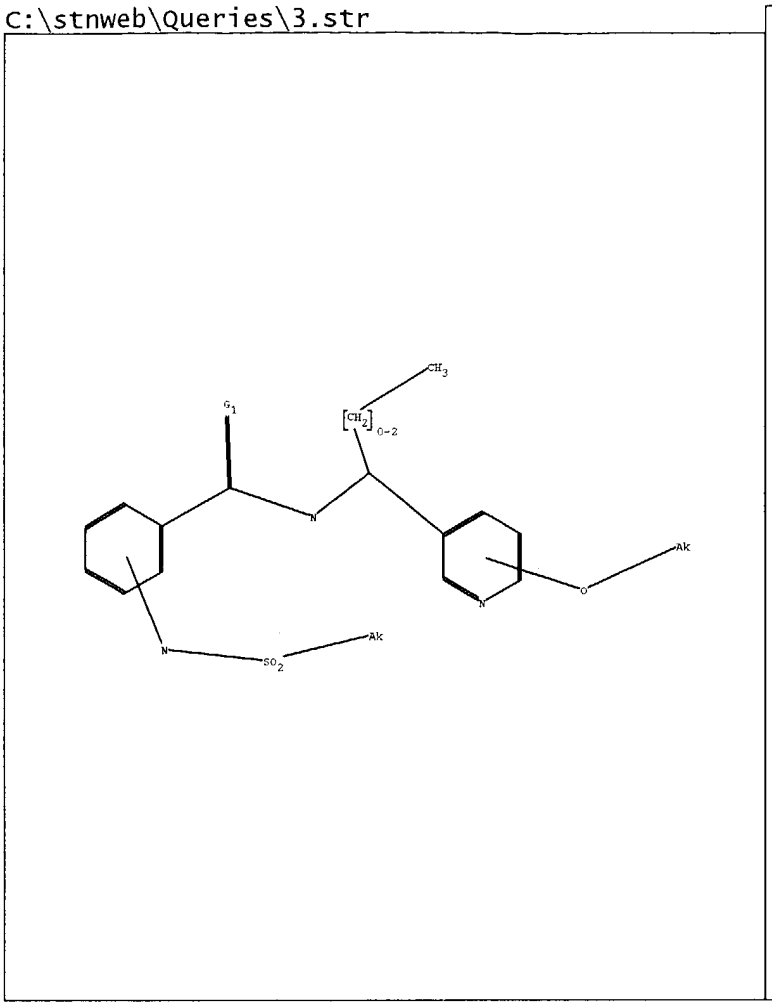


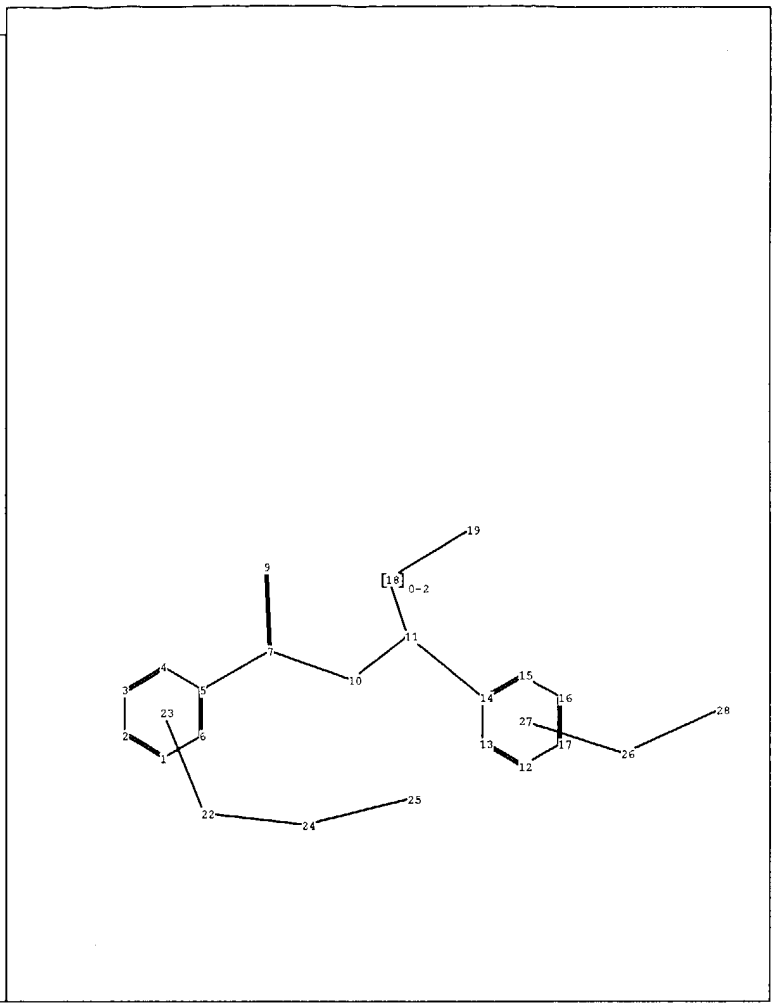


chain nodes :
7 9 10 11 18 19 22 24 25 26 28
ring nodes :
1 2 3 4 5 6 12 13 14 15 16 17
chain bonds :
5-7 7-9 7-10 10-11 11-14 11-18 18-19 22-24 24-25 26-28
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 12-13 12-17 13-14 14-15 15-16 16-17
exact/norm bonds :
7-9 7-10 10-11 22-24 24-25 26-28
exact bonds :
5-7 11-14 11-18 18-19
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 12-13 12-17 13-14 14-15 15-16 16-17
isolated ring systems :
containing 1 : 12 :

G1:O,S

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 9:CLASS 10:CLASS 11:CLASS
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:CLASS 22:CLASS
23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS

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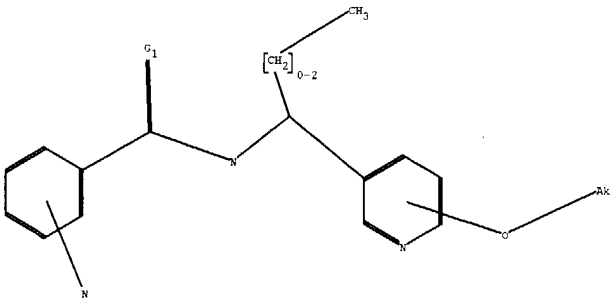


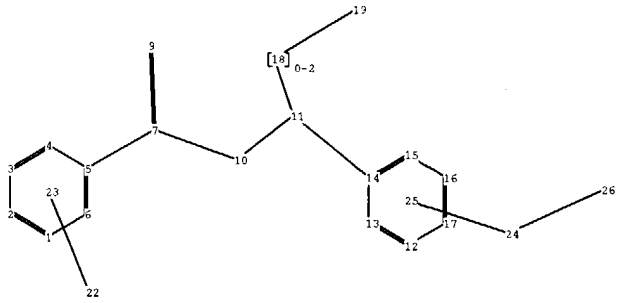


chain nodes :
7 9 10 11 18 19 22 24 26
ring nodes :
1 2 3 4 5 6 12 13 14 15 16 17
chain bonds :
5-7 7-9 7-10 10-11 11-14 11-18 18-19 24-26
ring bonds :
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exact/norm bonds :
7-9 7-10 10-11 24-26
exact bonds :
5-7 11-14 11-18 18-19
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 12-13 12-17 13-14 14-15 15-16 16-17
isolated ring systems :
containing 1 : 12 :

G1:O,S

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 9:CLASS 10:CLASS 11:CLASS
12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:CLASS 22:CLASS
23:CLASS 24:CLASS 25:CLASS 26:CLASS

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 NEWS EXPRESS  JULY 30 CURRENT WINDOWS VERSION IS V7.01, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004
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 NEWS INTER    General Internet Information
 NEWS LOGIN    Welcome Banner and News Items
 NEWS PHONE    Direct Dial and Telecommunication Network Access to STN
 NEWS WWW      CAS World Wide Web Site (general information)

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
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h eb c g cg b cg eb

FULL ESTIMATED COST 0.21 0.21

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STRUCTURE FILE UPDATES: 14 SEP 2004 HIGHEST RN 744786-72-9
DICTIONARY FILE UPDATES: 14 SEP 2004 HIGHEST RN 744786-72-9

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

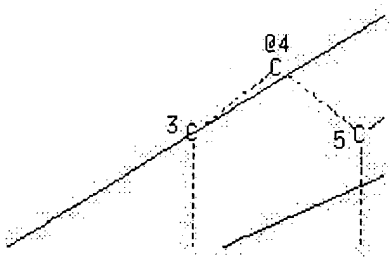
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
L1 STRUCTURE UPLOADED

=> l1
L1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d l1
L1 HAS NO ANSWERS
L1 STR
0 27 S 28

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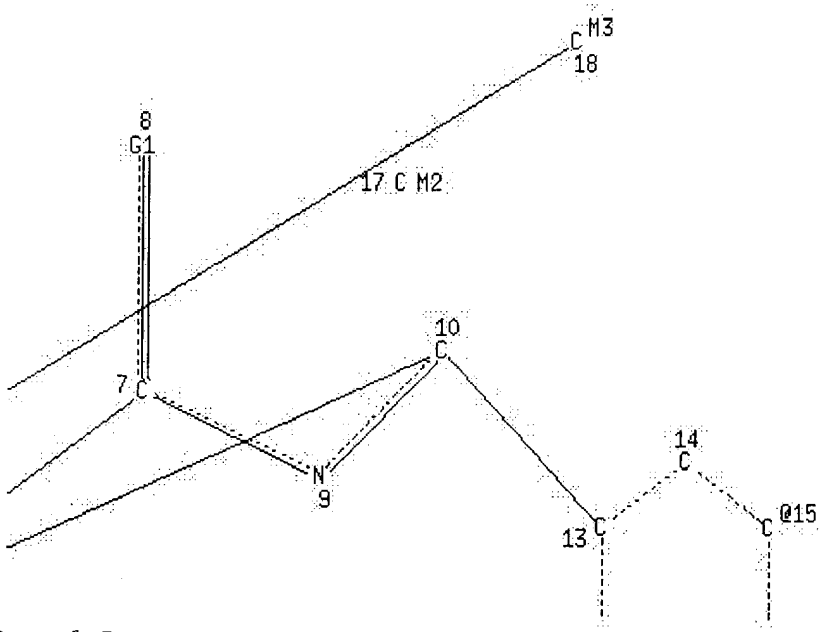
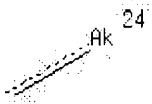
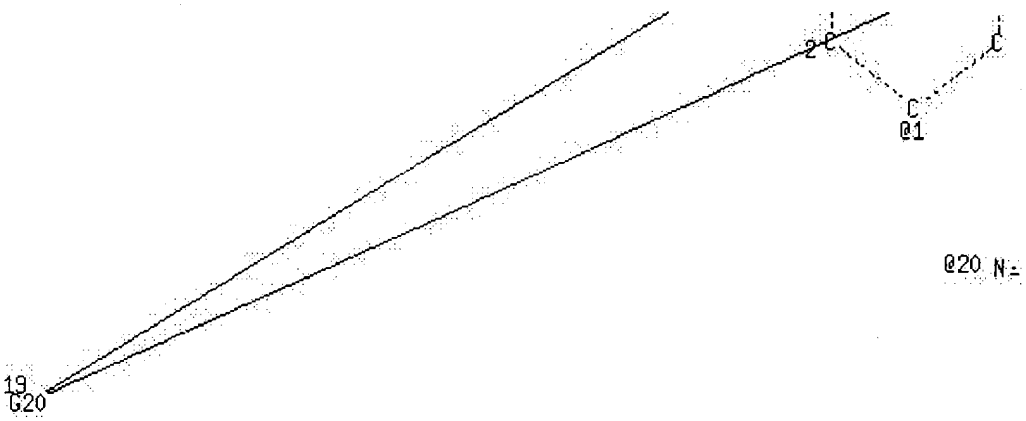
Page 1-A



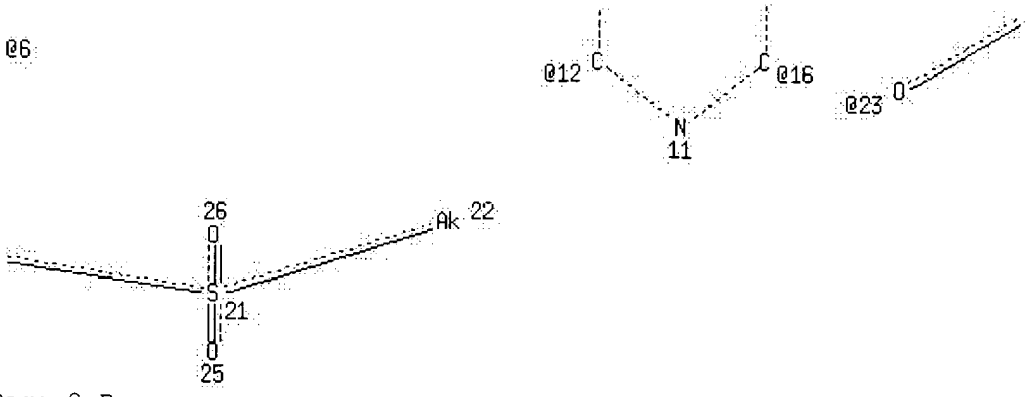

Page 1-B




Page 1-C




Page 2-A




Page 2-B

h eb c g cg b cg eb

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Page 2-C
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REP G20=(0-2) 17-10 17-18
VPA 20-1/4/6 S
VPA 23-12/15/16 S
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HCOUNT  IS M2     AT  17
HCOUNT  IS M3     AT  18
NSPEC   IS R      AT   1
NSPEC   IS R      AT   2
NSPEC   IS R      AT   3
NSPEC   IS R      AT   4
NSPEC   IS R      AT   5
NSPEC   IS R      AT   6
NSPEC   IS C      AT   7
NSPEC   IS C      AT   8
NSPEC   IS C      AT   9
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NSPEC   IS R      AT  11
NSPEC   IS R      AT  12
NSPEC   IS R      AT  13
NSPEC   IS R      AT  14
NSPEC   IS R      AT  15
NSPEC   IS R      AT  16
NSPEC   IS C      AT  17
NSPEC   IS C      AT  18
NSPEC   IS C      AT  19
NSPEC   IS C      AT  20
NSPEC   IS C      AT  21
NSPEC   IS C      AT  22
NSPEC   IS C      AT  23
NSPEC   IS C      AT  24
NSPEC   IS C      AT  25
NSPEC   IS C      AT  26
DEFAULT MLEVEL IS ATOM
MLEVEL  IS CLASS  AT   7  9 10 17 18 20 21 22 23 24 25 26 27 28
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  28

STEREO ATTRIBUTES: NONE


=> s l1
SAMPLE SEARCH INITIATED 20:36:14 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      1 TO ITERATE

100.0% PROCESSED       1 ITERATIONS                              0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:            1 TO        80
PROJECTED ANSWERS:               0 TO         0

L2            0 SEA SSS SAM L1

=> s l1 full
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h eb c g cg b cg eb

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THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 20:36:18 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -      23 TO ITERATE

100.0% PROCESSED      23 ITERATIONS                                  1 ANSWERS
SEARCH TIME: 00.00.01

L3             1 SEA SSS FUL L1

=> file hcaplus
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                                                         ENTRY     SESSION
FULL ESTIMATED COST                                     157.94      158.15

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FILE COVERS 1907 - 15 Sep 2004  VOL 141 ISS 12
FILE LAST UPDATED: 14 Sep 2004  (20040914/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> s l3
L4             1 L3

=> d l4, ibib abs fhitstr, 1

L4   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Cited References

```
ACCESSION NUMBER:          2002:849582  HCAPLUS
DOCUMENT NUMBER:           137:352782
TITLE:                     Preparation of anthranilic acid amides as
                           antiarrhythmics
INVENTOR(S):               Brendel, Joachim; Pirard, Bernard; Peukert, Stefan;
                           Kleemann, Heinz-Werner; Hemmerle, Horst
PATENT ASSIGNEE(S):        Aventis Pharma Deutschland GmbH, Germany
SOURCE:                    PCT Int. Appl., 111 pp.
                           CODEN: PIXXD2
DOCUMENT TYPE:             Patent
LANGUAGE:                  German
FAMILY ACC. NUM. COUNT:    1
PATENT INFORMATION:
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h eb c g cg b cg eb

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002088073 | A1 | 20021107 | WO 2002-EP4138 | 20020413 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10121003 | A1 | 20021219 | DE 2001-10121003 | 20010428 |
| EP 1385820 | A1 | 20040204 | EP 2002-742898 | 20020413 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| EE 200300529 | A | 20040216 | EE 2003-529 | 20020413 |
| BR 2002009185 | A | 20040803 | BR 2002-9185 | 20020413 |
| JP 2004527557 | T2 | 20040909 | JP 2002-585377 | 20020413 |
| US 2003187033 | A1 | 20031002 | US 2002-132163 | 20020426 |
| NO 2003004751 | A | 20031113 | NO 2003-4751 | 20031023 |
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| | | | WO 2002-EP4138 W | 20020413 |

OTHER SOURCE(S): MARPAT 137:352782
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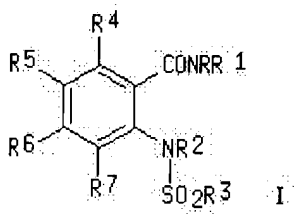

I

AB Title compds. [I; R = H, C1-4 alkyl, CpH2pR14, etc.; p = 0-5; R14 = cycloalkyl(substituted) (hetero)aryl; R1 = (branched) (unsatd.) (substituted) O-interrupted alkyl; R2 = H, C1-4 alkyl; R3 = C3-7 alkyl, C3-7 cycloalkyl, (substituted) naphthyl, Ph; R4-R7 = F, Cl, Br, I, CF3, OCF3, OCHF2, NO2, cyano, CO2Me, CONH2, COMe, OH, C1-4 alkyl, C1-4 alkoxy, N(Me)2, SO2NH2, NHSO2Me], were prepd. Thus, 0.6 mmol 2-phenylsulfonylamino-5-chlorobenzoyl chloride (prepn. given) was added to a mixt. of 0.66 mmol S-(-)-1-methylbenzylamine and 0.9 mmol Et3N in CH2Cl2 followed by stirring over night at room temp. to give 61 mg (S)-2-phenylsulfonylamino-5-chloro-N-(1-phenylethyl)benzamide. I act upon the Kv1.5 potassium channel and inhibit a potassium flow described as ultra-rapidly activating delayed rectifier in the human cardiac atrium. Tested I inhibited human Kv1.5 potassium flow in oocytes of Xenopus laevis with IC50 = 0.3->10 μM. β -Blockers and IKs-channel blockers can be used for the tablet formulation.

IT **474450-36-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of anthranilic acid amides as antiarrhythmics)

RN 474450-36-7 HCAPLUS

CN Benzamide, 2-[(butylsulfonyl)amino]-N-[1-(6-methoxy-3-pyridinyl)propyl]-(9CI) (CA INDEX NAME)

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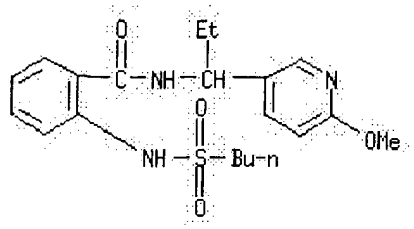

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file caold

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|---|---|---|
| FULL ESTIMATED COST | 7.12 | 165.27 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
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| CA SUBSCRIBER PRICE | -0.70 | -0.70 |

FILE 'CAOLD' ENTERED AT 20:36:32 ON 15 SEP 2004
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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> d his

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L3 1 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 20:36:21 ON 15 SEP 2004
L4 1 S L3

FILE 'CAOLD' ENTERED AT 20:36:32 ON 15 SEP 2004

=> s l3
L5 0 L3

=> file reg

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
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| FULL ESTIMATED COST | 0.42 | 165.69 |

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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   14 SEP 2004  HIGHEST RN 744786-72-9
DICTIONARY FILE UPDATES:  14 SEP 2004  HIGHEST RN 744786-72-9

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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L6 HAS NO ANSWERS
L6                STR
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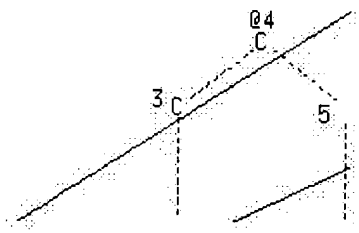


Page 1-A

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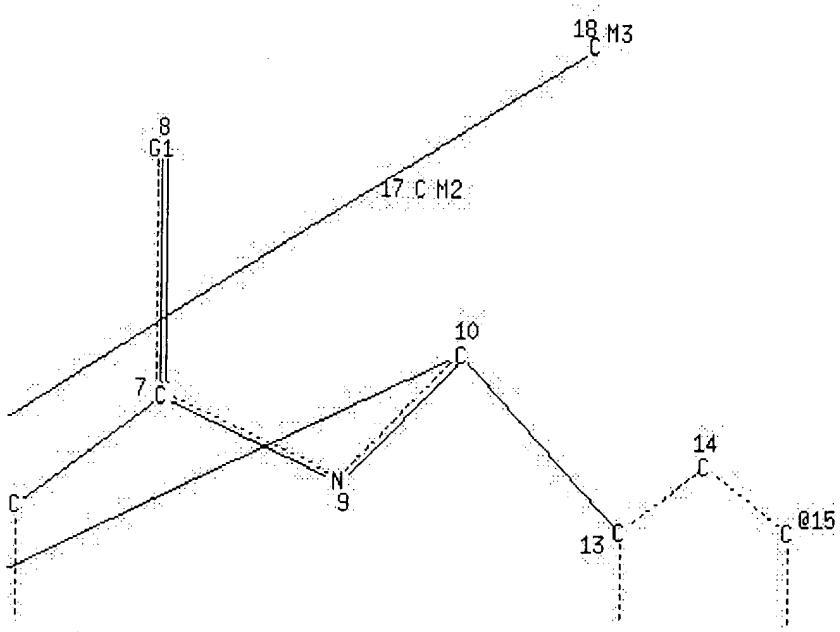
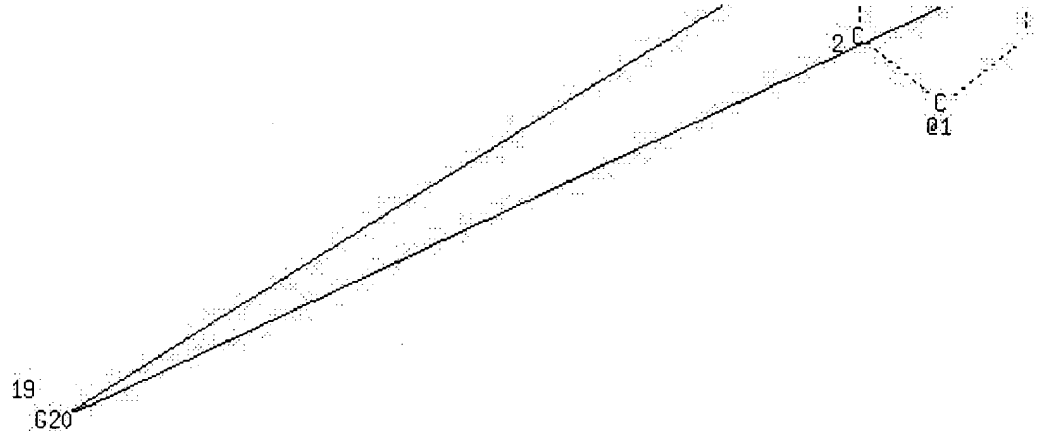
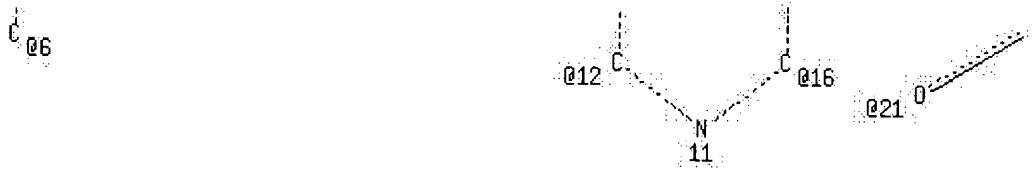



Page 1-B


Page 1-C




Page 2-A




N @20

Page 2-B

Page 2-C

VAR G1=23/24

REP G20=(0-2) 17-10 17-18

VPA 20-1/4/6 S

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VPA 21-12/15/16 S
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NSPEC   IS R      AT   2
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NSPEC   IS R      AT   4
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MLEVEL  IS CLASS  AT   7  9 10 17 18 20 21 22 23 24
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC I
NUMBER OF NODES IS  24

STEREO ATTRIBUTES: NONE


=> s l6
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SAMPLE SCREEN SEARCH COMPLETED -     97 TO ITERATE

100.0% PROCESSED      97 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         1350 TO     2530
PROJECTED ANSWERS:               0 TO        0

L7            0 SEA SSS SAM L6

=> s l6 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 155.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 20:37:24 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   2062 TO ITERATE

100.0% PROCESSED    2062 ITERATIONS                               4 ANSWERS
SEARCH TIME: 00.00.01
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h ebc gcg b cg eb

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L8             4 SEA SSS FUL L6

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   155.42     321.11

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00      -0.70

FILE 'HCAPLUS' ENTERED AT 20:37:29 ON 15 SEP 2004
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FILE COVERS 1907 - 15 Sep 2004  VOL 141 ISS 12
FILE LAST UPDATED: 14 Sep 2004  (20040914/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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L9             2 L8

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L3             1 S L1 FULL

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L4             1 S L3

     FILE 'CAOLD' ENTERED AT 20:36:32 ON 15 SEP 2004
L5             0 S L3

     FILE 'REGISTRY' ENTERED AT 20:36:37 ON 15 SEP 2004
L6               STRUCTURE UPLOADED
L7             0 S L6
L8             4 S L6 FULL

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L9             2 S L8
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h ebc gcgb cg eb

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L10             1 L9 NOT L4

=> d l10, ibib abs fhitstr, 1

L10  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2002:964322 HCAPLUS
DOCUMENT NUMBER: 138:24550
TITLE: Preparation of anthranilic acid amides as antiarrhythmics
INVENTOR(S): Brendel, Joachim; Boehme, Thomas; Peukert, Stefan; Kleemann, Heinz-Werner
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002100825 | A2 | 20021219 | WO 2002-EP5956 | 20020531 |
| WO 2002100825 | A3 | 20031211 | | |
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| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10128331 | A1 | 20021219 | DE 2001-10128331 | 20010612 |
| EE 200300558 | A | 20040216 | EE 2003-558 | 20020531 |
| EP 1399423 | A2 | 20040324 | EP 2002-745333 | 20020531 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| BR 2002010374 | A | 20040713 | BR 2002-10374 | 20020531 |
| US 2003114499 | A1 | 20030619 | US 2002-166595 | 20020612 |
| PRIORITY APPLN. INFO.: | | | DE 2001-10128331 A | 20010612 |
| | | | WO 2002-EP5956 W | 20020531 |

OTHER SOURCE(S): MARPAT 138:24550
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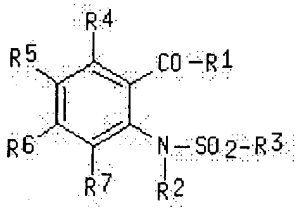


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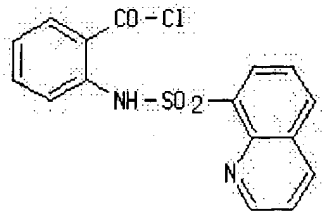


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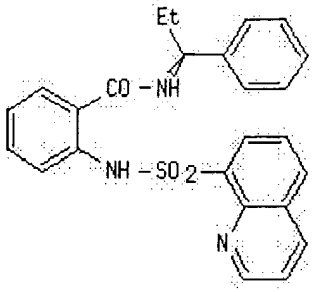



III

AB Title compds. I [R1 = NR8-C(R9)(R10)-A-O-E-R11, NR8-C(R9)(R12)-A-D-E-R11, NR13-C(R9)(R10)-A-D-E-R11, etc.; A = CnH2n; n = 0-5; D = bond, O; E = CmH2m; m = 0-5; R8 = H, alkyl, CpH2p-R14; p = 0-5; R14 = (un)substituted Ph, naphthyl, heteroaryl, etc.; R9 = H, alkyl; R10 = H, alkyl, (un)substituted Ph, etc.; R11 = cycloalkyl, (un)substituted Ph, naphthyl, etc.; R12 = alkyl, alkynyl, cycloalkyl, etc.; R13 = CpH2p-R14; R2 = H, alkyl; R3 = (un)substituted heteroaryl; R4, R5, R6, R7 = H, halo, CF3, etc.] and their pharmaceutically acceptable salts were prepd. For example, coupling of acid chloride II, e.g., prepd. from anthranilic acid in 2-steps, and (S)-1-phenylpropylamine afforded amide III. Compds. I act upon the Kv1.5 potassium channel and inhibit a potassium flow described as ultra-rapidly activating delayed rectifier in the human cardiac atrium.

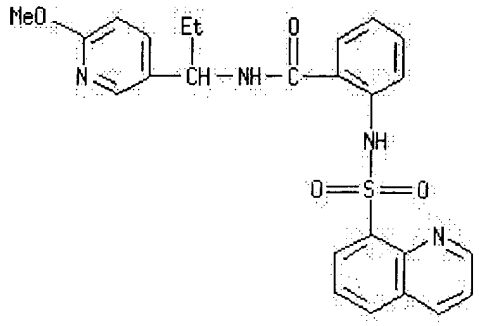
IT **478263-77-3P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; prepn. of anthranilic acid amides as antiarrhythmics)

RN 478263-77-3 HCAPLUS

CN Benzamide, N-[1-(6-methoxy-3-pyridinyl)propyl]-2-[(8-quinolinylsulfonyl)amino]- (9CI) (CA INDEX NAME)

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| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE | TOTAL |
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                                                          ENTRY     SESSION
CA SUBSCRIBER PRICE                                       -0.70       -1.40

FILE 'CAOLD' ENTERED AT 20:37:49 ON 15 SEP 2004
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FILE COVERS 1907-1966
FILE LAST UPDATED:  01 May 1997 (19970501/UP)

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  substance identification.  Title keywords, authors, patent
  assignees, and patent information, e.g., patent numbers, are
  now searchable from 1907-1966.  TIFF images of CA abstracts
  printed between 1907-1966 are available in the PAGE
  display formats.

  This file supports REGISTRY for direct browsing and searching of
  all substance data from the REGISTRY file.  Enter HELP FIRST for
  more information.

=> d his

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L2           0 S L1
L3           1 S L1 FULL

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L4           1 S L3

     FILE 'CAOLD' ENTERED AT 20:36:32 ON 15 SEP 2004
L5           0 S L3

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L6             STRUCTURE UPLOADED
L7           0 S L6
L8           4 S L6 FULL

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L9           2 S L8
L10          1 S L9 NOT L4

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L11          0 L8

=> file hcaplus
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CA SUBSCRIBER PRICE                                           0.00     -1.40
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FILE COVERS 1907 - 15 Sep 2004 VOL 141 ISS 12
FILE LAST UPDATED: 14 Sep 2004 (20040914/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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        542006 POTASSIUM
            15 POTASSIUMS
        542008 POTASSIUM
                 (POTASSIUM OR POTASSIUMS)
        307634 CHANNEL?
L12         82 ANTIARRHYTHMIC? (W) POTASSIUM (W) CHANNEL?

=> s l12 and inhibitor?
        893658 INHIBITOR?
L13         13 L12 AND INHIBITOR?

=> s l13 and review/dt
       1757748 REVIEW/DT
L14          2 L13 AND REVIEW/DT

=> d l14, ibib abs, 1-2

L14  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2002:949932 HCAPLUS
DOCUMENT NUMBER: 138:19049
TITLE: The immediate future for the medical treatment of atrial fibrillation
AUTHOR(S): Pedersen, Ole Dyg; Brendorp, Bente; Kober, Lars; Torp-Pedersen, Christian
CORPORATE SOURCE: Department of Cardiology, Gentofte University Hospital, Hellerup, 2100, Den.
SOURCE: Expert Opinion on Emerging Drugs (2002), 7(2), 259-268
CODEN: EOEDA3
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Atrial fibrillation is the most commonly sustained cardiac arrhythmia and a common reason for mortality and morbidity. Atrial

h eb c g cg b cg eb

fibrillation causes disease for three reasons: (i) the ventricular rate is often high, which leads to symptoms ranging from discomfort to life threatening heart failure; (ii) the rhythm causes loss of atrioventricular synchrony, which reduces diastolic filling and may lead to heart failure; and (iii) atrial contraction is lost leading to stagnant blood that again may lead to atrial thrombi and peripheral embolism. Thus, the treatment of atrial fibrillation is focused on the maintenance of sinus rhythm, rate control and prevention of embolism. For the maintenance of sinus rhythm, all drugs under current development are potassium channel blockers; the so-called class III anti-arrhythmic drugs. Those which have been further investigated appear to be valuable for maintenance of sinus rhythm but all carry a significant risk of pro-arrhythmia, in particular Torsade de Pointe ventricular tachycardia. Rate control has been a focus of treatment for many years and several very old drugs, including digoxin, are used for this. There is, to the author's knowledge, no current effort for evaluating new drugs for this indication. Prevention of embolism has for many years been obtained with vitamin K antagonists for which the clin. evidence is overwhelming. Previous attempts to replace vitamin K antagonists with aspirin have not been fruitful. A large no. of newer anticoagulation regimes are in development, but to the author's knowledge only a single thrombin **inhibitor** is actively being developed for atrial fibrillation.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2000:304412 HCAPLUS
DOCUMENT NUMBER: 132:302872
TITLE: Antiarrhythmic pharmacotherapy for the 21st century. Development of new K+ channel blockers
AUTHOR(S): Nakaya, Haruaki
CORPORATE SOURCE: Dep. Pharmacol., Chiba Univ. Sch. Med., Japan
SOURCE: Saishin Igaku (2000), 55(5), 1010-1016
CODEN: SAIGAK; ISSN: 0370-8241
PUBLISHER: Saishin Igakusha
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese

AB A review with 17 refs., on the structure and functional diversity of myocardial K+ channels, **inhibitory** effects of class III antiarrhythmic drugs on the K+ channels, ideal K+ channel blockers, and present status and future prospects of K+ channel blockers.

=> d his

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FILE 'REGISTRY' ENTERED AT 20:32:11 ON 15 SEP 2004
L1 STRUCTURE UPLOADED
L2 0 S L1
L3 1 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 20:36:21 ON 15 SEP 2004
L4 1 S L3

FILE 'CAOLD' ENTERED AT 20:36:32 ON 15 SEP 2004
L5 0 S L3

h eb c g cg b cg eb

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     FILE 'REGISTRY' ENTERED AT 20:36:37 ON 15 SEP 2004
L6                STRUCTURE UPLOADED
L7             0 S L6
L8             4 S L6 FULL

     FILE 'HCAPLUS' ENTERED AT 20:37:29 ON 15 SEP 2004
L9             2 S L8
L10            1 S L9 NOT L4

     FILE 'CAOLD' ENTERED AT 20:37:49 ON 15 SEP 2004
L11            0 S L8

     FILE 'HCAPLUS' ENTERED AT 20:39:28 ON 15 SEP 2004
L12           82 S ANTIARRHYTHMIC? () POTASSIUM () CHANNEL?
L13           13 S L12 AND INHIBITOR?
L14            2 S L13 AND REVIEW/DT

=> s l12 and block?
        527809 BLOCK?
L15         68 L12 AND BLOCK?

=> s l15 and review/dt
       1757748 REVIEW/DT
L16         14 L15 AND REVIEW/DT

=> s l16 not l13
L17         12 L16 NOT L13

=> d l17, ibib abs, 1-12

L17  ANSWER 1 OF 12  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2003:778983 HCAPLUS
DOCUMENT NUMBER: 140:138512
TITLE: **Blockers** of the Kv1.5 channel for the treatment of atrial arrhythmias
AUTHOR(S): Brendel, Joachim; Peukert, Stefan
CORPORATE SOURCE: Medicinal Chemistry, Aventis Pharma Deutschland GmbH, Frankfurt/Main, D-65926, Germany
SOURCE: Current Medicinal Chemistry: Cardiovascular & Hematological Agents (2003), 1(3), 273-287
CODEN: CMCCDP; ISSN: 1568-0169
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Atrial arrhythmias are a common problem in cardiol. practice. Despite the availability of several antiarrhythmic drugs, there is a medical need for safer and more efficient antiarrhythmic treatment. Compds. that act atrial selectively without prolonging the QTc-time and without neg. inotropy to terminate and / or prevent atrial arrhythmias would be of high interest. In this context, the voltage-gated potassium channel Kv1.5 is regarded as a promising target to achieve atrial selectivity, which in turn would be assocd. with fewer side effects than classical antiarrhythmics. This review summarizes patents and other publications on compds. which show this novel mode of action. The chem., selectivity and structure-activity data disclosed in the literature are discussed in light of recent work demonstrating the antiarrhythmic efficacy of Kv1.5 **blockers** in vivo. Several studies in pig, dog or goat models have confirmed their proposed atrial selective antiarrhythmic

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effect in vivo. Most of the more intensively characterized Kv1.5 **blockers** have turned out not to be selective but also **block** other ion channels. Based on the currently available data it seems that addnl. inhibition of Kv4.3 and KACh is beneficial for the desired antiarrhythmic effect or at least does not hamper the atrial selectivity of a Kv1.5 **blocker**. Significant **block** of IK1, HERG or sodium channels, however, clearly leads to loss of atrial selectivity and increases the risk of lethal ventricular proarrhythmia.

REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:12740 HCAPLUS
DOCUMENT NUMBER: 138:378418
TITLE: **Blockers** of the Kv1.5 channel for the treatment of atrial arrhythmias
AUTHOR(S): Brendel, Joachim; Peukert, Stefan
CORPORATE SOURCE: Medicinal Chemistry, G878, Aventis Pharma Deutschland GmbH, Frankfurt/Main, D-65926, Germany
SOURCE: Expert Opinion on Therapeutic Patents (2002), 12(11), 1589-1598
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Atrial arrhythmias are a common problem in cardiol. practice. Despite the availability of several antiarrhythmic drugs there is a medical need for safer and more efficient treatments. The voltage-gated potassium channel Kv1.5 is regarded as a promising target for the development of new atrial selective drugs with fewer side effects. This review summarizes patents claiming such compds. The chem. and biol. data disclosed in these patents are discussed in light of recent work demonstrating the antiarrhythmic effects of Kv1.5 **blockers** in vivo.

REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:290489 HCAPLUS
DOCUMENT NUMBER: 137:179233
TITLE: Animal models of lethal arrhythmias
AUTHOR(S): Billman, George E.
CORPORATE SOURCE: Department of Physiology and Cell Biology, The Ohio State University, Columbus, OH, 43210-1218, USA
SOURCE: Drug Development Research (2002), 55(1), 59-72
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Sudden cardiac death resulting from ventricular tachyarrhythmias remains the leading cause of death in industrially developed countries, accounting for between 300,000 and 500,000 deaths each year in the United States. Yet, despite the enormity of this problem, the development of safe and effective antiarrhythmic agents remains elusive. Indeed, several class I (encainide and flecainide) and class III (d-sotalol) drugs have actually been shown to increase, rather

h eb c g cg b cg eb

than decrease, the risk of arrhythmic death in patients recovering from myocardial infarction. The identification of effective antiarrhythmic agents is critically dependent on the use of appropriate animal models of human disease. In particular, myocardial ischemia may be an important determinant for the development of the life-threatening ventricular arrhythmias. For example, preclin. studies demonstrate that many drugs that prevent arrhythmias induced by programmed elec. stimulation fail to prevent ventricular fibrillation provoked by ischemia in the same animals. Thus, one would predict that animal models in which lethal arrhythmias are induced by myocardial ischemia would be the most effective tools for the identification of potential antiarrhythmic medications. This review first evaluates several animal models of lethal ventricular arrhythmias with particular emphasis placed on canine models. Then it closes with a brief discussion of ATP-sensitive potassium-channel antagonists as an example of antiarrhythmic drugs that may act selectively on the ischemic myocardium.

REFERENCE COUNT: 160 THERE ARE 160 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:41806 HCAPLUS
DOCUMENT NUMBER: 137:149522
TITLE: Clamikalant sodium: Antiarrhythmic KATP channel **blocker**
AUTHOR(S): Mealy, N. E.; Martin, L.; Castaner, J.
CORPORATE SOURCE: Prous Science, Barcelona, 08080, Spain
SOURCE: Drugs of the Future (2001), 26(10), 951-956
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review discussing the synthesis, pharmacol. actions, toxicol., pharmacokinetics and metab., and clin. studies of clamikalant sodium. Clamikalant sodium, which is currently in phase II clin. trials, was discovered to **block** cardiac ATP-sensitive potassium channels more effectively than pancreatic and vascular channels.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2001:588455 HCAPLUS
DOCUMENT NUMBER: 136:288373
TITLE: IKs channel **blockers**: potential antiarrhythmic agents
AUTHOR(S): Gerlach, U.
CORPORATE SOURCE: Medicinal Chemistry, Aventis Pharma Deutschland GmbH, Frankfurt/Main, D-65926, Germany
SOURCE: Drugs of the Future (2001), 26(5), 473-484
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review, with refs., discusses the different functions of IKs channel **blockers**, with emphasis on cardiac arrhythmias. Topics covered include ion channels in the heart; ion channel **blockers** as antiarrhythmic agents; mol. structure and function of the IKs channel; tissue species distribution of the IKs channel; selective IKs channel **blockers**; and

h eb c g cg b cg eb

drugs with IKs **blocking** activity as an addnl. effect.
REFERENCE COUNT: 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 6 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References

ACCESSION NUMBER: 2000:191638 HCAPLUS
DOCUMENT NUMBER: 133:68210
TITLE: Nifekalant, Mitsui
AUTHOR(S): Zaza, Antonio
CORPORATE SOURCE: University of Milan, Milan, 20133, Italy
SOURCE: Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs (2000), 2(1), 86-94
CODEN: CCPRFX; ISSN: 1464-8482
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with 120 refs., of the pharmacol. of nifekalant, a Class III (nonselective K+ channel **blocker**) antiarrhythmic agent that lacks β-**blocking** activity.
REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References

ACCESSION NUMBER: 1997:185324 HCAPLUS
DOCUMENT NUMBER: 126:194770
TITLE: Antiarrhythmic effects of K channel **blockers**
AUTHOR(S): Hagiwara, Nobuhisa; Kajimoto, Katsuya; Sakai, Rieko; Kasanuki, Hiroshi; Hosoda, Saichi
CORPORATE SOURCE: Dep. Cardiovascular Medicine, Heart Inst. of Japan, Japan
SOURCE: Kokyu to Junkan (1997), 45(2), 137-143
CODEN: KOJUA9; ISSN: 0452-3458
PUBLISHER: Igaku Shoin
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review, with 17 refs., discussing the antiarrhythmic effects of K channel **blockers**.

L17 ANSWER 8 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References

ACCESSION NUMBER: 1995:227957 HCAPLUS
DOCUMENT NUMBER: 122:144
TITLE: Potassium channel **blockers** as antiarrhythmic drugs
AUTHOR(S): Colatsky, Thomas J.; Argentieri, Thomas M.
CORPORATE SOURCE: Division Cardiovascular Diseases Diabetes, Wyeth-Ayerst Research, Princeton, NJ, 08543, USA
SOURCE: Drug Development Research (1994), 33(3), 235-49
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with >100 refs. Selective prolongation of cardiac repolarization is an effective means of suppressing a variety of cardiac arrhythmias,

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particularly those arising from a re-entrant mechanism. Over the past several years, a variety of novel compds. have been discovered that increase cardiac action potential duration without slowing conduction. Most of these agents (e.g., dofetilde, E-4031, MK-499) act by selectively **blocking** the rapidly activating component of delayed rectification (IKr), although some (e.g., ibutilide, azimilide, terikalant) have been proposed to work via alternate mechanisms. While the overall efficacy of these agents against tachyarrhythmias appears to be greater than obtained for the sodium channels **blockers**, primary concerns remain about the ability of these agents to prolong repolarization at fast heart rates (i.e., reverse use-dependence) and to exert proarrhythmic effects at slow heart rates (i.e., torsade de pointes). The limited clin. results obtained to date suggest that these potential limitations may be less important than previously thought, although clear pharmacodynamic differences among the various agents are beginning to emerge. While the effects of some class III agents on repolarization and refractoriness are clearly attenuated at rapid cycle lengths (e.g., sematilide, d-sotalol), the effects of others appear to be largely rate-independent, at least down to cycles as short as 350 ms. Also, the currently available data suggest that the risk of serious proarrhythmia may be lower (1-3%) and considerably more predictable than that seen during treatment with the class I agents. In summary, the rational design of selective **blockers** of cardiac K channels for development as antiarrhythmic drugs appears to have been relatively successful and continues to show considerable promise as a therapeutic approach.

L17 ANSWER 9 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1994:260301 HCAPLUS
DOCUMENT NUMBER: 120:260301
TITLE: Potassium channel **blockade** as an antiarrhythmic principle
AUTHOR(S): Mortensen, Elin; Yang, Tao; Refsum, Helge
CORPORATE SOURCE: Inst. Med. Biol., Univ. Tromso, Tromso, N-9037, Norway
SOURCE: Cardiovascular Drug Reviews (1993), 11(3), 370-84
CODEN: CDREEA; ISSN: 0897-5957
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 89 refs. Cardiac K+ channels and their physiol. role, antiarrhythmic mechanisms of K+ channel **blockers**, and K+ channel **blockade** in myocardial ischemia, heart failure, pos. inotropy, and heart rate are discussed.

L17 ANSWER 10 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1993:204515 HCAPLUS
DOCUMENT NUMBER: 118:204515
TITLE: Recent advances in antiarrhythmic therapy: Potassium channel antagonists
AUTHOR(S): Cimini, Madeline G.; Gibson, J. Kenneth
CORPORATE SOURCE: Upjohn Lab., Kalamazoo, MI, 49001, USA
SOURCE: Annual Reports in Medicinal Chemistry (1992), 27, 89-98
CODEN: ARMCBI; ISSN: 0065-7743
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 92 refs.

h eb c g cg b cg eb

L17 ANSWER 11 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1990:171527 HCAPLUS
DOCUMENT NUMBER: 112:171527
TITLE: Potassium channels in cardiac arrhythmias: focus on antiarrhythmic drug action
AUTHOR(S): Rials, Seth J.; Friehling, Ted D.; Marinchak, Roger A.; Kowey, Peter R.
CORPORATE SOURCE: Cardiac Arrhythmia Serv., Med. Coll. Pennsylvania, Philadelphia, PA, 19129, USA
SOURCE: Progress in Clinical and Biological Research (1990), Volume Date 1988, 334(Potassium Channels), 111-21
CODEN: PCBRD2; ISSN: 0361-7742
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 26 refs.

L17 ANSWER 12 OF 12 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1990:151089 HCAPLUS
DOCUMENT NUMBER: 112:151089
TITLE: Potassium channels as targets for antiarrhythmic drug action
AUTHOR(S): Colatsky, T. J.; Follmer, C. H.
CORPORATE SOURCE: Div. Exp. Ther., Wyeth-Ayerst Res., Princeton, NJ, 08543, USA
SOURCE: Drug Development Research (1990), 19(2), 129-40
CODEN: DDREDK; ISSN: 0272-4391
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with approx. 55 refs. on the role of K channel in the pharmacol. of antiarrhythmic agents. The class I agents have been shown to **block** cardiac sodium channels in a use-dependent manner, and the kinetics and potency of sodium channel **block** correlated with mol. wt. and lipid soly. of drug. The class IA agents, like quinidine, which increase cardiac action potential duration and refractory period in addn. to their effects on conduction, also appear to have potent **blocking** actions on the potassium channels responsible for repolarization in myocardial cells, whereas the class IB agents, like lidocaine, shorten action potential duration and are relatively specific in their **block** of sodium channels. In contrast, class III agents, which prolong the action potential without slowing conduction, appear to exert their primary **blocking** action on the potassium channel only. Conversion from class I to class III electrophysiol. profiles can be achieved by the substitution of electron-withdrawing groups (e.g., NO2) in place of electron-donating groups (e.g., NH2) on the arom. portion of the basic local anesthetic pharmacophore. Class III agents appear to be most effective against ventricular fibrillation and ventricular tachycardia due to re-entry, but are generally without activity in the 24 h Harris dog arrhythmia model.

=> d his

(FILE 'HOME' ENTERED AT 20:32:06 ON 15 SEP 2004)

FILE 'REGISTRY' ENTERED AT 20:32:11 ON 15 SEP 2004
L1 STRUCTURE UPLOADED
L2 0 S L1

h eb c g cg b cg eb

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L3              1 S L1 FULL

      FILE 'HCAPLUS' ENTERED AT 20:36:21 ON 15 SEP 2004
L4              1 S L3

      FILE 'CAOLD' ENTERED AT 20:36:32 ON 15 SEP 2004
L5              0 S L3

      FILE 'REGISTRY' ENTERED AT 20:36:37 ON 15 SEP 2004
L6                STRUCTURE UPLOADED
L7              0 S L6
L8              4 S L6 FULL

      FILE 'HCAPLUS' ENTERED AT 20:37:29 ON 15 SEP 2004
L9              2 S L8
L10             1 S L9 NOT L4

      FILE 'CAOLD' ENTERED AT 20:37:49 ON 15 SEP 2004
L11             0 S L8

      FILE 'HCAPLUS' ENTERED AT 20:39:28 ON 15 SEP 2004
L12            82 S ANTIARRHYTHMIC? () POTASSIUM () CHANNEL?
L13            13 S L12 AND INHIBITOR?
L14             2 S L13 AND REVIEW/DT
L15            68 S L12 AND BLOCK?
L16            14 S L15 AND REVIEW/DT
L17            12 S L16 NOT L13

=> s l12 and blocker?
         54106 BLOCKER?
L18         57 L12 AND BLOCKER?

=> s l18 and review/dt
       1757748 REVIEW/DT
L19         13 L18 AND REVIEW/DT

=> d l19, ibib abs, 1-13

L19  ANSWER 1 OF 13  HCAPLUS  COPYRIGHT 2004 ACS on STN
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Full Text | Citing References

ACCESSION NUMBER: 2003:778983 HCAPLUS
DOCUMENT NUMBER: 140:138512
TITLE: **Blockers** of the Kv1.5 channel for the treatment of atrial arrhythmias
AUTHOR(S): Brendel, Joachim; Peukert, Stefan
CORPORATE SOURCE: Medicinal Chemistry, Aventis Pharma Deutschland GmbH, Frankfurt/Main, D-65926, Germany
SOURCE: Current Medicinal Chemistry: Cardiovascular & Hematological Agents (2003), 1(3), 273-287
CODEN: CMCCDP; ISSN: 1568-0169
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Atrial arrhythmias are a common problem in cardiol. practice. Despite the availability of several antiarrhythmic drugs, there is a medical need for safer and more efficient antiarrhythmic treatment. Compds. that act atrial selectively without prolonging the QTc-time and without neg. inotropy to terminate and / or prevent atrial arrhythmias would be of high interest. In this context, the voltage-gated potassium

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channel Kv1.5 is regarded as a promising target to achieve atrial selectivity, which in turn would be assocd. with fewer side effects than classical antiarrhythmics. This review summarizes patents and other publications on compds. which show this novel mode of action. The chem., selectivity and structure-activity data disclosed in the literature are discussed in light of recent work demonstrating the antiarrhythmic efficacy of Kv1.5 **blockers** in vivo. Several studies in pig, dog or goat models have confirmed their proposed atrial selective antiarrhythmic effect in vivo. Most of the more intensively characterized Kv1.5 **blockers** have turned out not to be selective but also block other ion channels. Based on the currently available data it seems that addnl. inhibition of Kv4.3 and KACh is beneficial for the desired antiarrhythmic effect or at least does not hamper the atrial selectivity of a Kv1.5 **blocker**. Significant block of IK1, HERG or sodium channels, however, clearly leads to loss of atrial selectivity and increases the risk of lethal ventricular proarrhythmia.

REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2003:12740 HCAPLUS
DOCUMENT NUMBER: 138:378418
TITLE: **Blockers** of the Kv1.5 channel for the treatment of atrial arrhythmias
AUTHOR(S): Brendel, Joachim; Peukert, Stefan
CORPORATE SOURCE: Medicinal Chemistry, G878, Aventis Pharma Deutschland GmbH, Frankfurt/Main, D-65926, Germany
SOURCE: Expert Opinion on Therapeutic Patents (2002), 12(11), 1589-1598
CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Atrial arrhythmias are a common problem in cardiol. practice. Despite the availability of several antiarrhythmic drugs there is a medical need for safer and more efficient treatments. The voltage-gated potassium channel Kv1.5 is regarded as a promising target for the development of new atrial selective drugs with fewer side effects. This review summarizes patents claiming such compds. The chem. and biol. data disclosed in these patents are discussed in light of recent work demonstrating the antiarrhythmic effects of Kv1.5 **blockers** in vivo.

REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:949932 HCAPLUS
DOCUMENT NUMBER: 138:19049
TITLE: The immediate future for the medical treatment of atrial fibrillation
AUTHOR(S): Pedersen, Ole Dyg; Brendorp, Bente; Kober, Lars; Torp-Pedersen, Christian
CORPORATE SOURCE: Department of Cardiology, Gentofte University Hospital, Hellerup, 2100, Den.
SOURCE: Expert Opinion on Emerging Drugs (2002), 7(2), 259-268
CODEN: EOEDA3

h eb c g cg b cg eb

PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Atrial fibrillation is the most commonly sustained cardiac arrhythmia and a common reason for mortality and morbidity. Atrial fibrillation causes disease for three reasons: (i) the ventricular rate is often high, which leads to symptoms ranging from discomfort to life threatening heart failure; (ii) the rhythm causes loss of atrioventricular synchrony, which reduces diastolic filling and may lead to heart failure; and (iii) atrial contraction is lost leading to stagnant blood that again may lead to atrial thrombi and peripheral embolism. Thus, the treatment of atrial fibrillation is focused on the maintenance of sinus rhythm, rate control and prevention of embolism. For the maintenance of sinus rhythm, all drugs under current development are potassium channel **blockers**; the so-called class III anti-arrhythmic drugs. Those which have been further investigated appear to be valuable for maintenance of sinus rhythm but all carry a significant risk of pro-arrhythmia, in particular Torsade de Pointe ventricular tachycardia. Rate control has been a focus of treatment for many years and several very old drugs, including digoxin, are used for this. There is, to the author's knowledge, no current effort for evaluating new drugs for this indication. Prevention of embolism has for many years been obtained with vitamin K antagonists for which the clin. evidence is overwhelming. Previous attempts to replace vitamin K antagonists with aspirin have not been fruitful. A large no. of newer anticoagulation regimes are in development, but to the author's knowledge only a single thrombin inhibitor is actively being developed for atrial fibrillation.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 2002:290489 HCAPLUS
DOCUMENT NUMBER: 137:179233
TITLE: Animal models of lethal arrhythmias
AUTHOR(S): Billman, George E.
CORPORATE SOURCE: Department of Physiology and Cell Biology, The Ohio State University, Columbus, OH, 43210-1218, USA
SOURCE: Drug Development Research (2002), 55(1), 59-72
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review. Sudden cardiac death resulting from ventricular tachyarrhythmias remains the leading cause of death in industrially developed countries, accounting for between 300,000 and 500,000 deaths each year in the United States. Yet, despite the enormity of this problem, the development of safe and effective antiarrhythmic agents remains elusive. Indeed, several class I (encainide and flecainide) and class III (d-sotalol) drugs have actually been shown to increase, rather than decrease, the risk of arrhythmic death in patients recovering from myocardial infarction. The identification of effective antiarrhythmic agents is critically dependent on the use of appropriate animal models of human disease. In particular, myocardial ischemia may be an important determinant for the development of the life-threatening ventricular arrhythmias. For example, preclin. studies demonstrate that many drugs that prevent arrhythmias induced by programmed elec. stimulation fail to prevent ventricular fibrillation provoked by ischemia in the same animals. Thus, one would predict that animal models in which lethal arrhythmias are

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induced by myocardial ischemia would be the most effective tools for the identification of potential antiarrhythmic medications. This review first evaluates several animal models of lethal ventricular arrhythmias with particular emphasis placed on canine models. Then it closes with a brief discussion of ATP-sensitive potassium-channel antagonists as an example of antiarrhythmic drugs that may act selectively on the ischemic myocardium.
REFERENCE COUNT: 160 THERE ARE 160 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 5 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References

ACCESSION NUMBER: 2002:41806 HCAPLUS
DOCUMENT NUMBER: 137:149522
TITLE: Clamikalant sodium: Antiarrhythmic KATP channel **blocker**
AUTHOR(S): Mealy, N. E.; Martin, L.; Castaner, J.
CORPORATE SOURCE: Prous Science, Barcelona, 08080, Spain
SOURCE: Drugs of the Future (2001), 26(10), 951-956
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review discussing the synthesis, pharmacol. actions, toxicol., pharmacokinetics and metab., and clin. studies of clamikalant sodium. Clamikalant sodium, which is currently in phase II clin. trials, was discovered to block cardiac ATP-sensitive potassium channels more effectively than pancreatic and vascular channels.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 6 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References

ACCESSION NUMBER: 2001:588455 HCAPLUS
DOCUMENT NUMBER: 136:288373
TITLE: IKs channel **blockers**: potential antiarrhythmic agents
AUTHOR(S): Gerlach, U.
CORPORATE SOURCE: Medicinal Chemistry, Aventis Pharma Deutschland GmbH, Frankfurt/Main, D-65926, Germany
SOURCE: Drugs of the Future (2001), 26(5), 473-484
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with refs., discusses the different functions of IKs channel **blockers**, with emphasis on cardiac arrhythmias. Topics covered include ion channels in the heart; ion channel **blockers** as antiarrhythmic agents; mol. structure and function of the IKs channel; tissue species distribution of the IKs channel; selective IKs channel **blockers**; and drugs with IKs blocking activity as an addnl. effect.
REFERENCE COUNT: 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References

ACCESSION NUMBER: 2000:304412 HCAPLUS

h eb c g cg b cg eb

DOCUMENT NUMBER: 132:302872
TITLE: Antiarrhythmic pharmacotherapy for the 21st century. Development of new K+ channel **blockers**
AUTHOR(S): Nakaya, Haruaki
CORPORATE SOURCE: Dep. Pharmacol., Chiba Univ. Sch. Med., Japan
SOURCE: Saishin Igaku (2000), 55(5), 1010-1016
CODEN: SAIGAK; ISSN: 0370-8241
PUBLISHER: Saishin Igakusha
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review with 17 refs., on the structure and functional diversity of myocardial K+ channels, inhibitory effects of class III antiarrhythmic drugs on the K+ channels, ideal K+ channel **blockers**, and present status and future prospects of K+ channel **blockers**.

L19 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 2000:191638 HCAPLUS
DOCUMENT NUMBER: 133:68210
TITLE: Nifekalant, Mitsui
AUTHOR(S): Zaza, Antonio
CORPORATE SOURCE: University of Milan, Milan, 20133, Italy
SOURCE: Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs (2000), 2(1), 86-94
CODEN: CCPRFX; ISSN: 1464-8482
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review, with 120 refs., of the pharmacol. of nifekalant, a Class III (nonselective K+ channel **blocker**) antiarrhythmic agent that lacks β-blocking activity.
REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 1997:185324 HCAPLUS
DOCUMENT NUMBER: 126:194770
TITLE: Antiarrhythmic effects of K channel **blockers**
AUTHOR(S): Hagiwara, Nobuhisa; Kajimoto, Katsuya; Sakai, Rieko; Kasanuki, Hiroshi; Hosoda, Saichi
CORPORATE SOURCE: Dep. Cardiovascular Medicine, Heart Inst. of Japan, Japan
SOURCE: Kokyu to Junkan (1997), 45(2), 137-143
CODEN: KOJUA9; ISSN: 0452-3458
PUBLISHER: Igaku Shoin
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: Japanese
AB A review, with 17 refs., discussing the antiarrhythmic effects of K channel **blockers**.

L19 ANSWER 10 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN
Full Text | Citing References
ACCESSION NUMBER: 1995:227957 HCAPLUS
DOCUMENT NUMBER: 122:144
TITLE: Potassium channel **blockers** as antiarrhythmic drugs

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AUTHOR(S): Colatsky, Thomas J.; Argentieri, Thomas M.
CORPORATE SOURCE: Division Cardiovascular Diseases Diabetes, Wyeth-Ayerst Research, Princeton, NJ, 08543, USA
SOURCE: Drug Development Research (1994), 33(3), 235-49
CODEN: DDREDK; ISSN: 0272-4391
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with >100 refs. Selective prolongation of cardiac repolarization is an effective means of suppressing a variety of cardiac arrhythmias, particularly those arising from a re-entrant mechanism. Over the past several years, a variety of novel compds. have been discovered that increase cardiac action potential duration without slowing conduction. Most of these agents (e.g., dofetilde, E-4031, MK-499) act by selectively blocking the rapidly activating component of delayed rectification (IKr), although some (e.g., ibutilide, azimilide, terikalant) have been proposed to work via alternate mechanisms. While the overall efficacy of these agents against tachyarrhythmias appears to be greater than obtained for the sodium channels **blockers**, primary concerns remain about the ability of these agents to prolong repolarization at fast heart rates (i.e., reverse use-dependence) and to exert proarrhythmic effects at slow heart rates (i.e., torsade de pointes). The limited clin. results obtained to date suggest that these potential limitations may be less important than previously thought, although clear pharmacodynamic differences among the various agents are beginning to emerge. While the effects of some class III agents on repolarization and refractoriness are clearly attenuated at rapid cycle lengths (e.g., sematilide, d-sotalol), the effects of others appear to be largely rate-independent, at least down to cycles as short as 350 ms. Also, the currently available data suggest that the risk of serious proarrhythmia may be lower (1-3%) and considerably more predictable than that seen during treatment with the class I agents. In summary, the rational design of selective **blockers** of cardiac K channels for development as antiarrhythmic drugs appears to have been relatively successful and continues to show considerable promise as a therapeutic approach.

L19 ANSWER 11 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1994:260301 HCAPLUS
DOCUMENT NUMBER: 120:260301
TITLE: Potassium channel blockade as an antiarrhythmic principle
AUTHOR(S): Mortensen, Elin; Yang, Tao; Refsum, Helge
CORPORATE SOURCE: Inst. Med. Biol., Univ. Tromso, Tromso, N-9037, Norway
SOURCE: Cardiovascular Drug Reviews (1993), 11(3), 370-84
CODEN: CDREEA; ISSN: 0897-5957
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English

AB A review with 89 refs. Cardiac K+ channels and their physiol. role, antiarrhythmic mechanisms of K+ channel **blockers**, and K+ channel blockade in myocardial ischemia, heart failure, pos. inotropy, and heart rate are discussed.

L19 ANSWER 12 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1993:204515 HCAPLUS
DOCUMENT NUMBER: 118:204515
TITLE: Recent advances in antiarrhythmic therapy: Potassium

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channel antagonists
AUTHOR(S): Cimini, Madeline G.; Gibson, J. Kenneth
CORPORATE SOURCE: Upjohn Lab., Kalamazoo, MI, 49001, USA
SOURCE: Annual Reports in Medicinal Chemistry (1992), 27, 89-98
CODEN: ARMCBI; ISSN: 0065-7743
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 92 refs.

L19 ANSWER 13 OF 13 HCAPLUS COPYRIGHT 2004 ACS on STN

Full Text | Citing References

ACCESSION NUMBER: 1990:171527 HCAPLUS
DOCUMENT NUMBER: 112:171527
TITLE: Potassium channels in cardiac arrhythmias: focus on antiarrhythmic drug action
AUTHOR(S): Rials, Seth J.; Friehling, Ted D.; Marinchak, Roger A.; Kowey, Peter R.
CORPORATE SOURCE: Cardiac Arrhythmia Serv., Med. Coll. Pennsylvania, Philadelphia, PA, 19129, USA
SOURCE: Progress in Clinical and Biological Research (1990), Volume Date 1988, 334(Potassium Channels), 111-21
CODEN: PCBRD2; ISSN: 0361-7742
DOCUMENT TYPE: Journal; **General Review**
LANGUAGE: English
AB A review with 26 refs.

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USA. The antiarrhythmics of classes I and III customary at present reduce the reoccurrence rate of AF, but are only used restrictively because of their potential proarrhythmic side effects. There is therefore a great medical need for the development of better medicaments for the treatment of atrial arrhythmias (S. Nattel, Am. Heart J. 130, 1995, 1094 - 1106; "Newer developments in the management of atrial fibrillation").

It has been shown that most supraventricular arrhythmias are subject to "reentry" excitation waves. Such reentries occur when the cardiac tissue possesses a slow conductivity and at the same time very short refractory periods. The increase in the myocardial refractory period due to prolongation of the action potential is a recognized mechanism for ending arrhythmias or preventing their formation (T. J. Colatsky et al., Drug Dev. Res. 19, 1990, 129 - 140; "Potassium channels as targets for antiarrhythmic drug action"). The length of the action potential is essentially determined by the extent of repolarizing $K^+$ currents which flow out of the cell via various $K^+$ channels. Particularly great importance is ascribed here to the "delayed rectifier" IK, which consists of 3 different components: $IK_r$, $IK_s$ and $IK_{ur}$.

Most known class III antiarrhythmics (for example dofetilide, E4031 and d-sotalol) mainly or exclusively block the rapidly activating potassium channel $IK_r$, which can be detected both in cells of the human ventricle and in the atrium. It has been shown, however, that these compounds have an increased proarrhythmic risk at low or normal heart rates, arrhythmias, which are described as "torsades de pointes", in particular being observed (D. M. Roden, Am. J. Cardiol. 72, 1993, 44B – 49B; "Current status of class III antiarrhythmic drug therapy"). Beside this high and in some cases fatal risk at a low rate, a decrease in the activity under the conditions of tachycardia, in which the action is needed in particular, was found for the $IK_r$ blockers ("negative use dependence").

The "particularly rapidly" activating and very slowly inactivating component of the delayed rectifier $IK_{ur}$ (= ultra-rapidly activating delayed rectifier), which corresponds